

NEW ANALOGS OF TETRAHYDROCANNABINOL

BY

MORTON HARFENIST

B.S., The College of the City of New York, 1942

M.S., The Polytechnic Institute of Brooklyn, 1946

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
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ACKNOWLEDGMENT

The author wishes to acknowledge his indebtedness to Professor Roger Adams, who suggested this problem and supervised its development.

He would also like to express his gratitude for a teaching assistantship, granted him from September, 1946 to February, 1947, and for University Fellowships received from June, 1947 to June, 1948.

He wishes to thank Mrs. J. L. Johnson for several infra-red absorption spectra, and J. C. Brantley and Dorothy D. Brantley for a number of ultra-violet absorption spectra.



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INTRODUCTION

The hemp plant, *Cannabis sativa*, is used as an intoxicant in many parts of the world, preparations being known variously as marihuana, charas, hashish, ganja, bhang, etc. The active component, which has been named tetrahydrocannabinol, has been shown to be a 1-hydroxy-3-*n*-amyl-6,6,9-trimethyltetrahydro-6-dibenzopyrane. The highest-numbered ring contains one double bond, probably in the 7,8 position.

Although a pure sample of tetrahydrocannabinol has not yet been synthesized, previous workers have shown that analogous compounds, which have the double bond common to the cyclohexane and pyrane rings and a wide variety of 3-alkyl substituents replacing the *n*-amyl group, have marihuana activity. This activity is increased markedly by the presence of branchings in the side chain. The most active compound encountered, the 3-(1,2-dimethylheptyl) analog, displays activity nearly seventy times that of the purest material obtained from natural sources.

The purpose of this work was to prepare some additional branched-chain analogs of tetrahydrocannabinol.

DISCUSSION OF RESULTS

To determine whether the extremely active compound, 1-hydroxy-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran represented the structure leading to the maximum of marihuana activity in the 1,2-dimethylalkyl series, the 3-(1,2-dimethylhexyl), and the 3-(1,2-dimethyloctyl) "conjugated tetrahydrocannabinols" were prepared. The method was that used for the related compound, with minor changes(1). The reaction of the Grignard reagent of 2-bromoöctane with 3,5-dimethoxybenzamide gave 2-(3,5-dimethoxybenzoyl)octane, which was purified by means of

Girard's reagent. The ketone was treated with methyl magnesium iodide to give the carbinol, which was dehydrated by heating with a catalytic amount of acid. Reduction of 2-(3,5-dimethoxyphenyl)-3-methyl-2-nonene with copper chromite and hydrogen was followed by demethylation to the alkylresorcinol by means of hydrobromic acid in acetic acid. It was found that the extent of reduction could be followed by the ultra-violet absorption at a wave-length of about 247 m. μ . The alkylresorcinol was cyclized by treatment with ethyl 5-methylcyclohexanone-2-carboxylate and phosphorous oxychloride to 1-hydroxy-3-(1,2-dimethyloctyl)-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone, which, upon treatment with methyl magnesium iodide, gave 1-hydroxy-3-(1,2-dimethyloctyl)-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran. The 3-(1,2-dimethylhexyl) analog was prepared from 2-bromohexane similarly.

As preliminary values of the activities of these analogs showed that the maximum had been attained in the 1,2-dimethylheptyl compound, experiments directed at the synthesis of a 3-(1,2,3-trimethylalkyl) analog were instituted. The method outlined above was unsuccessful because of the low yield of Grignard reagent from 3-methyl-2-bromoöctane. It was possible to prepare α -3,5-dimethoxyphenethyl methyl ketone by the reaction of 3,5-dimethoxyhydratropionitrile with the methyl Grignard reagent, but the main reaction was reduction, rather than addition, when the ketone was treated with a Grignard reagent prepared from 2-bromopentane. An attempt to prepare the desired alkylresorcinol was undertaken by the Reformatsky reaction (2) of 3,5-dimethoxyacetophenone and ethyl 2-bromopropionate, followed by dehydration with hydrogen chloride of the ethyl 2-methyl-3-hydroxy-3-(3,5-dimethoxyphenyl)butyrate. Catalytic reduction of the ester was supplemented by a sodium amalgam reduction of the acid. It was not possible to prepare a pure sample of 2-(3,5-dimethoxyphenyl)-3-methyl-4-heptanone by condensing the substituted butyryl chloride with propyl cadmium.

The synthesis of the 3-(1,2,4-trimethylhexyl) pyrone was carried out by a series of steps involving reduction of 3,5-dimethoxybenzoic acid to the benzyl alcohol with lithium aluminum hydride (3), conversion of the alcohol to 3,5-dimethoxyphenylacetonitrile (1), carbethoxylation to the aryl cyanoacetic ester by means of ethyl carbonate (4), methylation with methyl iodide and a sodium alkoxide to yield α -carbethoxy-3,5-dimethoxyhydratropo-nitrile, and saponification of that to 3,5-dimethoxyhydratropo-nitrile. The nitrile, on treatment with the Grignard reagent of 2-methyl-1-bromobutane, gave 2-(3,5-dimethoxyphenyl)-5-methyl-3-heptanone, which was converted by treatment with methyl magnesium iodide and subsequent dehydration by the Chugaev method and reduction with Raney nickel and hydrogen, to 2-(3,5-dimethoxyphenyl)-3,5-dimethylheptane. This resorcinyll ether was demethylated to the 5-alkylresorcinol, which was cyclized to 1-hydroxy-3-(1,2,4-trimethylhexyl)-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone. This compound has not yet crystallized.

An attempt to form a pyrone from 3,5-dihydroxyphenyl butyl carbinol, made by a lithium aluminum hydride reduction of the ketone, was unsuccessful.

The synthesis of other compounds potentially capable of transformation to branched-chain analogs of tetrahydrocannabinol has also been undertaken.

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VITA

The author was born in New York, N. Y., on December 6, 1922, and attended the public schools there. He was admitted to the College of the City of New York in February, 1939, and received the Bachelor of Science degree in September, 1942. He held Tremaine scholarships for one and one-half years.

He was employed as a research assistant at Wallace and Tiernan Products, Belleville, N. J. until March, 1943, and as a research chemist at the Wellcome Research Laboratories, Tuckahoe, N. Y., from then until his induction into the United States Navy in March, 1944. During this time he took evening graduate courses at the Polytechnic Institute of Brooklyn.

About one and one-half years of his navy career were spent at the Naval Medical Research Institute, Bethesda, Md., working with the chemistry and physiology groups.

Upon his discharge in March, 1946, he returned to the Polytechnic Institute of Brooklyn, and completed his work for the Master of Science degree in June, 1946.

He has been enrolled at the University of Illinois since September, 1946, and has been a teaching assistant, and the recipient of University Fellowships.



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